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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,669	04/30/2001	Philippe Marliere	205907USOPCT	9510

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
 1940 DUKE STREET
 ALEXANDRIA, VA 22314

EXAMINER

LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/830,669

Applicant(s)

MARLIERE ET AL.

Examiner

Gerald G Leffers Jr., PhD

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 52-85 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 52, 53, 55-72 and 74-85 is/are rejected.
- 7) ☒ Claim(s) 54 and 73 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 4/21/2004, in which several claims were amended (claims 52-53, 61, 63, 68, 70, 75 and 85). Claims 52-85 are pending in the instant application.

Any rejection of record in the previous office action not addressed herein is withdrawn. This action is not final due to additional grounds of rejection made herein that could have been made in the previous action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69-72, 74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection similar to the grounds of rejection made in the previous office action, mailed 10/21/2003.**

The rejected claims are drawn to host cells obtained by methods of selection wherein a missense mutation is incorporated into a an essential gene required for growth of the host cell and the cell is grown under selective conditions wherein 1) the culture medium does not contain a nutrient that will compensate for the lack of a functional copy of the essential gene product,

Art Unit: 1636

and 2) the culture medium contains an amino acid not encoded by the missense mutation and which will restore functional activity when incorporated into the mutated protein. Claims 69, 71-72 and 74 encompass any mutant of any gene that will compensate for the loss of the essential gene product. For example, loss of an essential drug resistance marker might be compensated for by the generation of a "leaky" mutant of a protein pump on the cell surface. Thus, rejected claims 69, 71-72 and 74 encompass a number of different mutants that do not necessarily include mutants of a tRNA-synthase gene corresponding to the missense codon and which would differ depending upon the nature of the essential gene. The instant specification and prior art appear to only describe embodiments wherein a mutant tRNA synthase gene is identified that can incorporate a non-canonical amino acid into an essential protein and do not provide a basis to envision what other types of mutations might occur in a cell that compensate for the loss of a given essential protein. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims (e.g. for claim 70 which does actually recite the presence of a mutated aminoacyl-tRNA synthetase in the claimed cell).

Response to Arguments/112 1st Rejection

Applicant's arguments filed on 4/21/2004 have been fully considered but they are not persuasive. The response essentially argues 1) the present invention implicitly requires mutated aminoacyl tRNA synthetases for obtaining mutated target proteins, 2) the mutations of the tRNA synthetases have no direct effect on the life and growth of the cells, 3) the aminoacyl-tRNA synthetase mutations are not necessarily essential for the survival of the cell and the precise

Art Unit: 1636

nature of these mutations is not necessary for implementing the invention, 4) the instant specification clearly discloses that it is not necessary for practicing the methods of selection to know in advance the mutation of the aminoacyl-tRNA synthetase in the cells, 5) missense mutations introduced into the target codon are introduced into a gene encoding a protein that is essential for the life of the cell, 6) these mutations are well defined in the specification, 7) the introduction of missense mutations into a given gene sequence was well known at the time of the invention, 8) the response points to post-filing art by applicants that discloses new results using the methods recited in the pending claims.

The response appears to be arguing limitations that are not present in the claims (i.e. the invention does not implicitly require a mutated aminoacyl-tRNA synthetase). There is no limitation in claims 69, 71-72 and 74 that the mutation that allows growth of the selected cells is necessarily in an aminoacyl-tRNA synthetase gene. Even for claim 70, which does explicitly require the presence of a mutated aminoacyl-tRNA synthetase, there is no means for one of skill in the art to envision the particular mutation that allows the aminoacyl-tRNA synthetase gene to meet the functional limitations of the claims. Therefore, the skilled artisan would not have been able to envision a sufficient number of specific embodiments of such mutated proteins to describe the broadly claimed genus of host cells comprising the mutated proteins.

With regard to the remainder of the arguments, the examiner fully understands that it is not necessary to know beforehand the exact nature of the aminoacyl-tRNA synthetase mutants in order to practice the methods used to obtain such mutants. A structural/functional basis for being able to envision the mutations obtained by such selection techniques as are recited in claim 52 is required in order to be able to envision a sufficient number of specific embodiments of such

Art Unit: 1636

mutants to describe the broadly claimed genus. Neither the instant specification nor the prior art provide such a correlation between structure and function, whether for aminoacyl-tRNA synthetase mutants or other, non-synthetase mutants (e.g. like the “leaky” channel postulated above).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52-53, 55-72, 74-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is vague and indefinite in that the preamble of the claim, provision of cells with the capacity to produce a mutated protein, is not necessarily recapitulated by practicing the recited methods steps. This makes it unclear as the claim is currently written when one has satisfied all of the claim limitations, after simply performing the methods steps whatever the outcome, or performing the methods steps until the objective stated in the preamble as in fact been achieved. **This is a new rejection.**

Claims 67-68 are vague and indefinite in that there is no clear and positive prior antecedent basis for the term “aminoacyl-tRNA synthetase” in the claims upon which they are dependent. **This is a new rejection.**

Claim 70 is vague and indefinite in that it is not clear how one would necessarily be able to determine whether a gene sequence encoding a mutated aminoacyl-tRNA synthetase possesses

Art Unit: 1636

a mutation introduced by genetic recombination techniques or one not involving genetic recombination techniques. **This is a new rejection.**

Claim 85 is vague and indefinite in that the metes and bounds of the phrase "further comprising functionalizing the isolated protein" are unclear. The term "functionalizing" appears to be defined in the instant specification with regard to the incorporation of noncanonical amino acids into the primary sequence of a given protein such that the protein acquires new properties (e.g. ability to be purified based on a selective property conveyed by the side group(s) of the noncanonical amino acid(s) (e.g. page 15, lines 1-28). It is unclear then how the cited phrase further limits claim 75 which already recites a method that results in the incorporation of noncanonical amino acids. Does the phrase mean that additional rounds of selection/incorporation are required, or that some other manipulation of the isolated protein is intended?

Conclusion

No claims are allowed. Claims 54 and 73 are objected to as being dependent upon rejected claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1636

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

ggl


GERRY LEFFERS
PRIMARY EXAMINER